THE KISHNER REDUCTION-ELIMINATION

BY

SAMUEL GELFAND

B. S., Yale University, 1950

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AN ABSTRACT OF A THESIS

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FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN CHEMISTRY
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THE KISHNER REDUCTION-ELIMINATION

Introduction

The discovery by Leonard and Sentz (1) that the Wolff-Kishner reduction of 1,2-dimethyl-1-azacycloöctan-3-one led anomalously to a mixture of N-methyloctenylamines as the major product has led to an extensive study of the scope and limitations of this reaction. Although this was the first example of the elimination of an α-amino substituent which has been observed, scattered examples of the elimination during the course of Wolff-Kishner reduction of certain other α-substituents have been reported.

Discussion

The behavior, under Wolff-Kishner conditions, of representative six- and seven-membered cyclic α-aminoketones, 1-methyl-2-ethyl-3-piperidone (1) and 1,2-dimethyl-1-azacycloheptan-3-one (II), was studied to determine the effect of variation of ring-size on the extent of elimination. The Huang-Minlon modification of the Wolff-Kishner reaction (2) was used for these reductions, as it was for all the reductions carried out in this investigation. The only product obtained from the reduction of I was the "normal" reduction product, 1-methyl-2-ethylpiperidine, while the mixture of products from II contained 44% of acyclic unsaturated amines as determined by the quantitative catalytic hydrogenation of a freshly distilled sample of the product.

The generality of the Kishner reduction-elimination was determined by a study of the reduction of a group of available or readily accessible acyclic α-substituted ketones. The following compounds were reduced: α-phenyl-α'-N-piperidylacetone, α-phenyl-α-N-piperidylacetone, α-phenyl-α-N-anilinoactetone, α-N-piperidylpropiophenone, α-phenyl-α-N-piperidylacetophenone, α-p-methoxyphenyl-N-α-phenylethylamino - p - methoxyacetophenone, benzoin ethyl ether, and 1-amyloxy-3-phenylacetone. For the α-aminoketones the extent of elimination varied over wide limits depending on the structure of the aminoketone, while for both alkoxyketones elimination was

the predominant reaction.

The α-substituted pinacolone series, $(CH_3)_3CCOCH_2Y$ (III), was selected for a study of the extent of elimination for different α-amino substituents and for the extension of the reaction to α-substituents, the elimination of which had not been previously observed. For a series of substituted piperidinoketones, III; Y= piperidino<α-methylpiperidino, α,α′-dimethylpiperidino, the extent of elimination increased with increasing steric hindrance about the C-N bond. The α,α,α′,α′-tetramethylpiperidinoketone was not reduced under these conditions, probably because the aminoketone is too hindered to form a hydrazone readily (3). The extent of elimination also increased with increase in ring-size for cyclic α-amino substituents, III; Y= pyrrolidino < piperidino <hexamethyleneimino. Elimination in varying amounts was also observed for other α-amino substituents, III; Y= *n*-heptylamino, anilino, N-methylanilino, di-*n*-butylamino, α-α-dimethylpyrrolidino.

The extension of the reaction to other α-substituents was limited by the instability of certain α-substituted ketones to the strongly alkaline conditions of the reaction. Extensive elimination was observed for the following other α-substituted pinacolones: III; Y= phenoxy, phenylmercapto, *n*-hexylmercapto, mesitoyloxy, trimethylacetyloxy.

That the elimination takes place through reaction of the intermediate hydrazone was confirmed by the observation that for representative α-substituted pinacolones substantially the same results were obtained from the reaction of the ketone with hydrazine and potassium hydroxide in solution and by the alkaline decomposition of the preformed hydrazone.

The establishment of the reaction as a new type of base-catalyzed elimination reaction and other possible reaction mechanisms are discussed.

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VITA

The author was born in Norwich, Connecticut on January 28, 1927. He attended public schools there, and was graduated from the Norwich Free Academy in June, 1944. He attended Yale University from July, to December, 1944 and the University of Connecticut from January, to March, 1945 as a member of the Army Specialized Training Program. He served on active duty in the United States Army from April, 1945 to December, 1946. Upon discharge he re-entered Yale University and received the degree of Bachelor of Science in Chemistry in June, 1950. He entered the Graduate College of the University of Illinois in September, 1950. He held a University Fellowship during the academic year 1951-1952, a U. S. Rubber Company Fellowship during the academic year 1952-1953, and Sinclair Refining Company Fellowships during the summers of 1952 and 1953.